Screening for Cardiovascular Risk (2/6/09)

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Introduction

Cardiovascular disease is the biggest killer in the UK causing 198,000 deaths per year and stroke is the most common cause of disability in women. Can individuals at increased risk be identified and can heart attacks and strokes be prevented?

Traditional methods of risk assessment for premature events (heart attacks and strokes) use conventional risk, factors such as smoking, high blood pressure and blood cholesterol to calculate risk often expressed as the 10 year Framingham Risk Score (FRS). However, these methods are far from perfect. Although they identify high risk groups, if followed up these high risk groups contain at best only 40% of the events that will occur in the subsequent 10 years. The rest occur in the low risk groups. Why? We now know that 50% of those who develop heart attacks and strokes do not have any of the conventional risk factors.

Screening and improved selection of individuals for more effective prevention is now possible because: (a) preclinical (silent) deposits of cholesterol in the arteries known as plaques develop slowly over several decades before they rupture or obstruct an artery becoming clinically manifest, (b) screening methods are now available for detecting the presence and severity of such plaques and (c) current prophylaxis with aggressive risk factor modification can reduce morbidity and mortality from heart attacks and strokes by 50%.

Screening for Preclinical Arterial Disease

Two methods are currently popular: (a) coronary artery calcium scoring (CACS) using multislice CT-scanning known as Electron Beam Tomography (EBT) and (b) ultrasonic arterial scanning. Each method provides information that can improve the FRS. This editorial summarises the efficacy of each method and associated advantages and disadvantages in an attempt to answer the questions which method or combination of methods and when should be used, and most importantly what advice should be given to individuals once the results become available.

CACS using multislice CT-scanning

Six prospective studies have demonstrated that coronary artery calcium score (CACS) obtained by computed tomography is an independent predictor of future coronary events (1) i.e. it provides information over and above that of the FRS. The risk of annual fatal myocardial infarction (MI) for CACS less than 100 is low (< 0.4%), for CACS 100-400 it is moderate (1.3%) and for CACS 400 or higher it is high (2.4%). Although CACS is a good predictor of coronary artery disease, it cannot identify those with non-calcific unstable plaques responsible for most of the heart attacks (1). Also, the finding of a high CACS in the absence of any significant coronary artery stenosis (> 50%) is common indicating the need to improve predictive ability.

On the basis of the available data the American College of Cardiology Foundation and American Heart Association have stated in their guidelines (1) that screening is of limited clinical value in individuals who are at low risk for coronary events i.e. FRS less than 1.0% per year. However, in individuals with a FRS of 1-2% (10-20% in 10 years) the finding of CACS of 400 or higher would increase the risk to that noted with diabetes or peripheral arterial disease (2). Thus, clinical decision making could be altered by CACS measurement in individuals with an intermediate FRS. Individuals with a high FRS (≥ 2%) should be treated aggressively according to the current NCEP III guidelines and do not require additional testing (2). The current literature does not support the concept that high-risk asymptomatic individuals can be safely excluded from prophylaxis even if CACS is zero.

A disadvantage of CACS is that it is expensive and the high radiation dose associated with it does not allow repeated testing. Also, CACS does not provide information on stroke risk.

Screening with ultrasound

High resolution ultrasound can provide images of the arterial wall and plaques with measurements of intima-media thickness (IMT), plaque thickness and plaque area at a resolution of 0.2 mm. Several studies (3) have indicated that IMT can be used to study the effect of risk factor modification in large groups and has become a validated biomarker. However, it is only marginally better than conventional risk factors in identifying individuals at increased risk. Thus, IMT is not a helpful test for risk assessment in individuals. However, new ultrasonic arterial wall measurements such

as the presence and thickness of plaques (4-6) and plaque echolucency (6-8) not only in the carotid but also in the common femoral have been shown to be stronger predictors of risk with a relative risk (RR) of 3.0 to 5.0.

Two prospective studies have shown that carotid plaque area is a better predictor of future myocardial infarction than IMT (9-10). In the Tromsø study (9), IMT, total plaque area and plaque echolucency were measured in 6226 men and women aged 25 to 84 years with no previous MI followed for 6 years. The adjusted RR and 95% CI between the highest plaque area tertile versus no plaque was 1.56 (1.04 to 2.36) in men and 3.95 (2.16 to 7.19) in women. The adjusted corresponding RR and 95% CI for IMT was 1.73 (0.98 to 3.06) in men and 2.86 (1.07 to 7.65) in women. Plaque echolucency (low collagen content) indicating plaque instability was also associated with increased risk of MI. In the study performed in Canada (10) carotid plaque areas from 1686 patients followed for up to 5 years were categorised into 4 quartiles. The combined 5 year risk of stroke, myocardial infarction and vascular death by quartiles of plaque area was: 5.6%, 10.7%, 13.9% and 19.5%.

In our own ongoing study, 2000 individuals over the age of 40 are being screened for conventional risk factors, clinical and preclinical cardiovascular disease and followed-up for 5 years (11). Both carotid and both common femoral bifurcations are scanned with ultrasound. In the first 762 individuals, evidence of clinical cardiovascular disease was present in 113 (14.8%). After adjustment for conventional risk factors the association of total plaque area (TPA) (sum of all plaque areas) with prevalence of clinical cardiovascular disease was high (Odds Ratio of upper to lower TPA quintile: 8.38; 95% CI 2.57 to 27.32). TPA greater than 42 mm^2 (cut-point derived from ROC curve analysis) identified 266 (34.9%) of the population that contained 87/113 (76.9%) of the clinical events (sensitivity: 77%; specificity: 73%; positive predictive value: 33%; negative predictive value: 94%). Thus, the presence and size of preclinical plaques in both carotid and both common femoral arteries is emerging as having a strong association with coronary heart disease and stroke.

Advantages of screening with ultrasound are the relatively low cost and absence of radiation. It can be performed in 30 minutes. In addition, it can be repeated at 6-monthly intervals or annually providing information on plaque progression or regression. An added benefit of ultrasound is that with the addition of an extra 5-10 minutes, men over the age of 65 can be screened for the presence of abdominal aortic aneurysm as recently recommended by NICE.

A rational screening plan

a). Individuals with low FRS: should be screened with ultrasound. Absence of plaques found in 50% of individuals in this low risk group will confirm the low risk and further follow-up with ultrasound will not be necessary for 3 to 4 years. However, the presence of plaques found in the other 50% will result in reclassification to a higher risk and will prompt the clinician to advise not only on risk factor modification but also to look for non conventional risk factors such as elevated homocysteine. Two recent prospective randomised controlled trials in individuals with known cardiovascular disease have demonstrated that lowering homocysteine with vitamin supplements has reduced the risk of ischemic stroke by 25% (12, 13).

b). Individuals with an intermediate FRS: should be initially screened with ultrasound. Those with plaques are advised to have aggressive risk factor modification. They are told that plaques should not be allowed to progress and that regression, which with treatment to target can occur in 28%, is associated with a 50% reduction in risk (10). They are also advised to have an annual ECG stress test. If plaques are absent then CACS may be performed. The latter will allow reclassification to a lower or higher risk group with confidence.

c). Individuals with a high FRS: are advised to have aggressive risk factor modification according to the current guidelines. Screening with ultrasound in order to follow plaque progression or regression is optional. This and the associated plaque images provide a strong incentive to persevere with prophylactic therapy as compliance can be challenging.

This screening strategy uses a combination of conventional risk factors with ultrasound which is in the forefront of noninvasive, inexpensive imaging modalities for screening asymptomatic individuals. It should go a long way towards achieving the government target of reducing heart attacks and strokes by 40% (14) even within the primary care arena.

*For information on the work of the CDER Trust apply to: The Secretary, CDER Trust, UK registered charity, 37 Rosedene Ave, Greenford, Middlesex, UB6 9SD, UK

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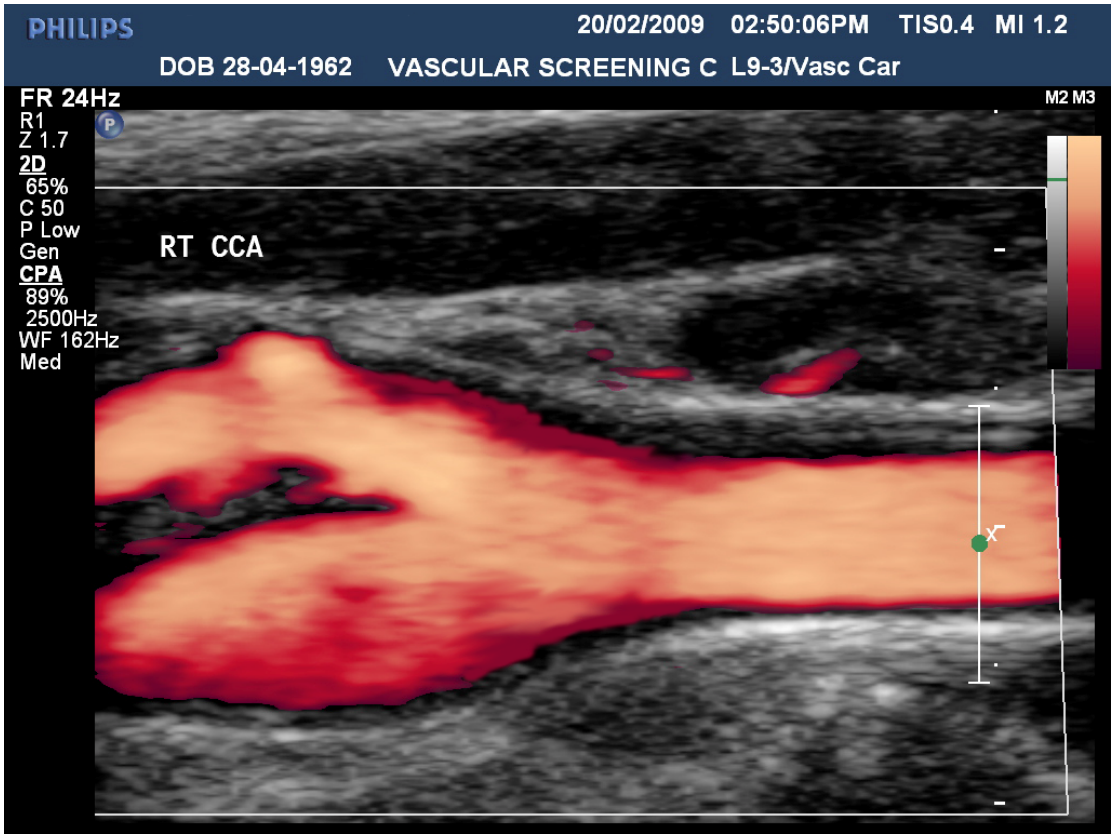

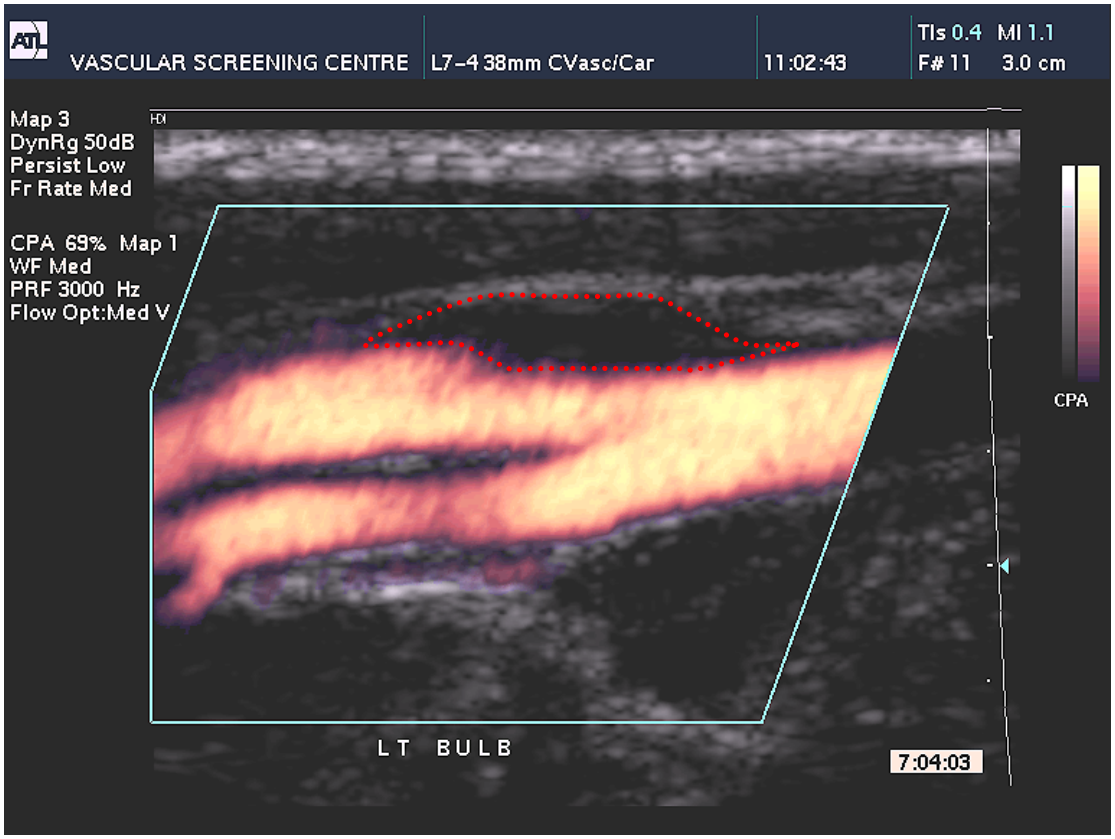

A normal carotid bifurcation with blood flow shown in red and a bifurcation with a plaque outlined by a red dotted line.